Received: 2 March 2023 | Revised: 16 June 2023 | Accepted: 24 July 2023

DOI: 10.1002/psp4.13024

ARTICLE

Model based assessment of food and acid reducing agent effects on oral absorption of mezigdomide (CC-92480), a novel cereblon E3 ligase modulator

Fan Wu | **Liangang Liu** | **Allison Gaudy** | **Xiaomin Wang** | **Leon Carayannopoulos** | **Michael Pourdehnad** | **Manisha Lamba**

Bristol Myers Squibb, Princeton, New Jersey, USA

Correspondence
Fan Wu, Bristol Myers Squibb, 100 Nassau Park Blvd #300, Princeton, NJ 08540, USA.
Email: fan.wu@bms.com

Abstract

Mezigdomide is a novel cereblon E3 ligase modulator (CELMoD) agent with enhanced autonomous cell-killing activity in multiple myeloma (MM) cells, and promising immunomodulatory and antitumor activity in patients with MM. We developed a population pharmacokinetics (PKs) model for mezigdomide in healthy subjects (HSs), and quantified effects of high-fat meal and proton pump inhibitor (PPI) on human disposition parameters. Plasma concentrations from 64 HS in two phase I clinical studies (NCT03803644 and NCT04211545) were used to develop a population PK model. The HSs received single oral doses of 0.4–3.2 mg mezigdomide with full PK profiles collected. A two-compartment linear PK model with first-order absorption and lag time best described mezigdomide PK profiles in HSs. The population PK parameters of absorption rate constant, lag time, central volume of distribution, clearance, peripheral volume of distribution, and intercompartmental clearance were estimated to be 1.18 h^{-1} (interoccasion variability [IOV]: 65%), 0.423 h (IOV: 31%), 440 L (interindividual variability [IIV]: 63%), 35.1 L/h (IIV: 40%), 243 L (IIV: 26%), and 36.8 L/h (IIV: 26%), respectively. High-fat meal increased oral bioavailability by ~30% and PPI co-administration decreased oral bioavailability by ~64%. Mezigdomide demonstrated a linear dose-exposure relationship in HSs. The PK model suggests a modest effect of high-fat meal, and a substantial effect of PPIs on mezigdomide oral bioavailability. This population PK model enables data integration across studies to identify important covariate effects and is being used to guide dose selection in clinical study designs for mezigdomide in patients with MM.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Mezigdomide is a novel CELMoD agent with strong immunomodulatory and promising antitumor activity in patients with multiple myeloma and is currently under clinical development.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can a population pharmacokinetic (PK) framework be used to characterize mezigdomide PK parameters and integrate assessment of food and proton pump inhibitor (PPI) effects on PK parameters using pooled data from two phase I clinical studies in healthy subjects (HSs)?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Plasma PK profiles of mezigdomide of HSs were adequately described by a two-compartment oral PK model with first-order absorption model incorporating a lag time in absorption and first-order elimination model. Covariate analyses revealed a modest food effect and substantial PPI effect on relative bioavailability of mezigdomide.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The population PK model captures overall dose-exposure trend and associated variability, provides a systematic framework to integrate data across studies, quantifies simultaneous evaluation of extrinsic factors that can influence rate and extent of relative bioavailability, and is being used to guide dose adjustments for mezigdomide in clinical studies.

INTRODUCTION

Mezigdomide (CC-92480) is a potent, novel cereblon E3 ligase modulator (CELMoD) agent designed for rapid and maximal degradation of target proteins, including Ikaros and Aiolos.[1] Mezigdomide has cell-specific effects and induces potent cell-autonomous killing of myeloma cells, as well as immune stimulation.[1,2]

Mezigdomide has demonstrated encouraging clinical activity and a manageable safety profile in heavily pretreated patients with relapsed or refractory multiple myeloma (MM) in combination with dexamethasone, as well as in combination with standard-of-care therapies.[3,4] Two phase III trials of mezigdomide in combination with proteasome inhibitors (i.e., bortezomib plus dexamethasone and carfilzomib plus dexamethasone) are currently underway.[5,6] With a dissociation constant of 6, mezigdomide is a weak-base compound with pH-dependent solubility (data on file). Solubility at pH 1 is 0.133 mg/mL, which decreases ~100-fold to 0.001 mg/mL at pH 5. These physicochemical attributes make mezigdomide potentially susceptible to food and effects of acid-reducing agents (ARAs) on absorption processes in patients. An understanding of the potential impact of these extrinsic factors is critical to optimize the intended therapeutic effects of mezigdomide.

To support clinical evaluation of food on mezigdomide pharmacokinetics (PKs), a phase I study (Study I, NCT03803644) was conducted to investigate the safety, tolerability, PKs, pharmacodynamics, and food effect of single ascending doses of mezigdomide in healthy subjects (HSs). Another phase I study (Study II, NCT04211545) was conducted to evaluate the impact of ARAs that included a proton pump inhibitor (PPI) on the PKs of mezigdomide in HSs, and to evaluate the relative bioavailability between two formulations of mezigdomide. Rabeprazole, a long-acting PPI, was evaluated as the ARA in the second study.

METHODS

Population and data collection

Plasma concentration from 64 HSs in two phase I clinical studies (Studies I and II) was used in this population PK analysis. Subjects were either women of non-childbearing potential or men. Discontinued subjects were replaced at the discretion of the investigator and the sponsor's medical monitor. The presence of any of the following excluded a subject from enrollment: history of any clinically significant and relevant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychological, pulmonary,

metabolic, endocrine, hematological, or allergic disease, drug allergies, or other major disorders as determined by the investigator; and any prior medical treatment or pre-existing conditions potentially altering the PKs of mezigdomide in vivo.

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. Before the start of the study, the study protocol, informed consent form, and any other appropriate documents were approved by the Institutional Review Board (Table S1). The investigator obtained informed consent from all subjects prior to any study-related procedures.

Study designs

In Study I, HSs received escalating single oral doses of 0.4–3.2 mg mezigdomide, or placebo in the fasted state ($N=6$ per dose group received mezigdomide) in a parallel design (Figure 1). For the food-effect evaluation, which was part 2 of this study, HSs received single 0.8-mg oral doses with a US Food and Drug Administration (FDA)-standard[7] high-fat, high-calorie meal, or under fasted conditions ($N=16$ in the food-effect arm), in a crossover fashion. In Study II, HSs ($N=24$) received a test and reference formulation at single oral dose of 1.6 mg mezigdomide in the fasted state, in a randomized crossover design (Figure 1). For the relative bioavailability (F) assessment, HSs received formulation A ($N=22$) or formulation B ($N=23$) in the absence of a PPI. For the PPI assessment, HSs received formulation A ($N=16$) or formulation B ($N=16$) in the presence of the long-acting PPI, rabeprazole, administered for at least 7 days before mezigdomide to maximize acid reduction potential. Serial PK samples were collected from all HSs. Here, formulation A represents a reference formulation used in the first-in-human trials and formulation B represents a test formulation of mezigdomide.

Bioanalytic method

To determine human plasma samples for concentrations of mezigdomide (S-enantiomer and CC-92480)

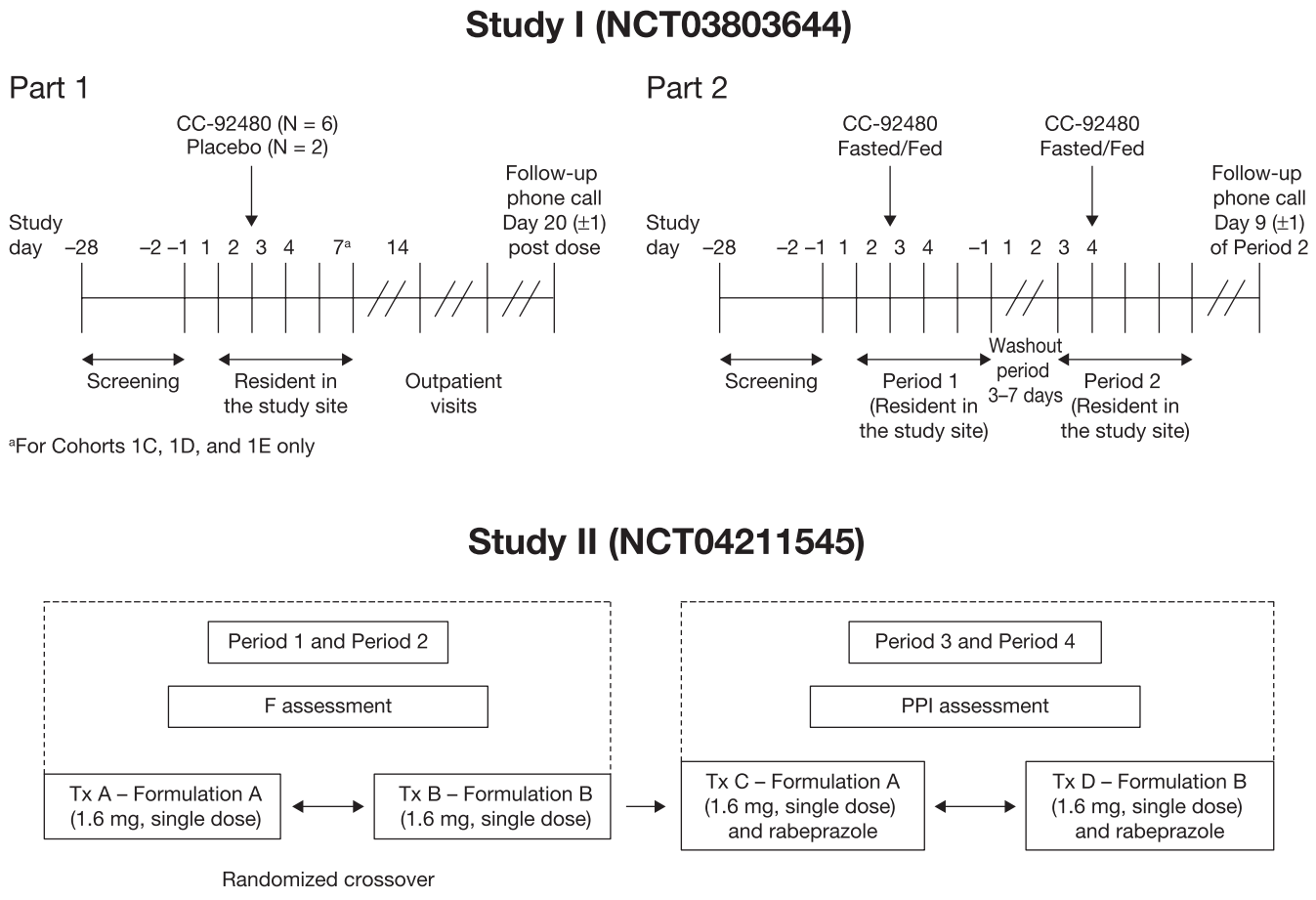

FIGURE 1 Study designs. F, relative bioavailability; formulation A, test formulation; formulation B, reference formulation; PPI, proton pump inhibitor; Tx, treatment.

and its R-enantiomer (CC-0982796) in human plasma supplemented with K2 EDTA, a validated chiral liquid chromatography–tandem mass spectrometry assay was utilized. The method utilized solid phase extraction (SPE; 96-well SPE [Strata-X, 50 mg/well], Phenomenex) to extract CC0777374 (the racemic mixture of mezigdomide and its R-enantiomer) and its deuterated internal standard (CC0994635) from 250 µL of human plasma. After transfer to a new plate, the solvent was evaporated and the samples were reconstituted and injected for liquid chromatography–tandem mass spectrometry analysis using a chiral column (Chiralpak AS-RH [2.1 × 150 mm, 5 µm]). Positive ions were measured in the multiple reaction monitoring mode using a SciexAPI-6500 tandem mass spectrometer (AB-Sciex) equipped with a Turbo Ion Spray source. The lower limit of quantification (LLOQ) was 0.05 ng/mL for both mezigdomide and its R-enantiomer, with linearity demonstrated to 20 ng/mL.

Model development and methodology

For purposes of the population PK model, data from both studies were pooled as patient characteristics were similar between them. The population PK analysis and model performance evaluation were conducted in Monolix (version 2020R1; Lixoft SAS) using the software-supplied stochastic approximation expectation–maximization (SAEM) algorithm. The additional post-processing and diagnostic analyses on the results were conducted in RStudio (version 1.4.1103-4; Posit Software, PBS). The plasma concentrations of mezigdomide collected from the two clinical studies were used in the modeling analysis from the PK modeling data set.

By examining the model fitting and performance, the base model was selected to be a two-compartment model with first-order oral absorption, a lag time in absorption (T_{lag}), and first-order elimination from the central compartment (Figure S1). The structural model parameters include relative bioavailability, absorption rate constant (k_a), T_{lag}, distribution volume of the central compartment ($V1$), clearance (CL), distribution volume of the peripheral compartment ($V2$), and intercompartmental clearance (Q). The relative bioavailability assessment was incorporated to estimate the impacts of formulation B (test formulation), food, and the co-administration of PPI. In addition, random effects were incorporated into the structural model to account for interindividual variability (IIV) and interoccasional variability (IOV), that is, the within-subject variability between treatment periods. The structural, random effects, and error models are described in (Text S1).

The covariate model was developed by adding covariates according to the diagnostic plots and statistical tests provided in Monolix and examining modeling performance after incorporating the covariate effects into the base model. The covariates that were explored in model building included age, body weight, serum creatinine level, sex, race, food, formulation, and co-administration with PPI. No apparent correlation was observed between the candidate covariates (Text S2). Following the stepwise covariate building approach as suggested in Traynard et al.,[8] the covariate effect was included into the final model when the difference in corrected Bayesian Information Criterion (BICc) from the previous optimal run decreased (ΔBICc < 0). The final population PK model included the covariate effect of food on F, T_{lag}, and k_a, along with the covariate effects of PPI on F and k_a, and formulation on F.

In the final model, the covariate effect on structural model parameters were expressed as:

$$\log(F) = \log\left(F_{pop}\right) + \beta_{F,\mathrm{FOOD}} \bullet \mathrm{FOOD} + \beta_{F,\mathrm{PPI}} \bullet \mathrm{PPI} + \beta_{F,\mathrm{FORMU}} \bullet \mathrm{FORMU}$$

$$\log\left(k_a\right) = \log\left(k_{a_{pop}}\right) + \beta_{k_a,\mathrm{FOOD}} \bullet \mathrm{FOOD} + \beta_{k_a,\mathrm{PPIA}} \bullet \mathrm{PPIA} + \beta_{k_a,\mathrm{PPIB}} \bullet \mathrm{PPIB} + \eta_{\mathrm{OCC},k_a}$$

$$\log\left(T_{lag}\right) = \log\left(Tlag_{pop}\right) + \beta_{T_{lag},\mathrm{FOOD}} \bullet \mathrm{FOOD} + \eta_{\mathrm{OCC},T_{lag}}$$

$$\log(\mathrm{CL}) = \log\left(\mathrm{CL}_{pop}\right) + \eta_{\mathrm{ID,CL}}$$

$$\log(V1) = \log\left(V1_{pop}\right) + \eta_{\mathrm{ID},V1}$$

$$\log(Q) = \log\left(Q_{pop}\right) + \eta_{\mathrm{ID},Q}$$

$$\log(V2) = \log\left(V2_{pop}\right) + \eta_{\mathrm{ID},V2}$$

where, F represents relative bioavailability, β represents the model estimated effects for the respective covariate effect, η_{ID} represents random effect at the individual level, and η_{OCC} represents combined random effects at the occasion and individual level.

FOOD = 1 if a high-fat meal is given or otherwise 0, PPI = 1 if mezigdomide is co-dosed with a PPI or otherwise 0, PPIA = 1 if mezigdomide is co-dosed in formulation A with a PPI or otherwise 0; PPIB = 1 if mezigdomide is co-dosed in formulation B with a PPI or otherwise 0; FORMU = 0 if mezigdomide is dosed in formulation A and FORMU = 1 if in formulation B.

Model performance evaluation

The model performance was evaluated based on scientific plausibility, BICc, log-likelihood, goodness of

fit, visual predictive check (VPC) plot, following the Monolix modeling workflow recommended by Traynard et al.[8] In addition, nonparametric bootstrap resampling was conducted using the R package Rsmlx (version 3.0.3 on GitHub; Posit Software, PBS) that was installed in R (version R4.0.3). The robustness of convergence was examined using the convergence assessment tool included in Monolix.

RESULTS

Demographics

The PK modeling data were collected from 64 HS, including 40 in Study I and 24 in Study II, with demographic characteristics summarized in Table 1. The subjects had a mean (range) age of 38.5 (18–55) years, a mean (range) height of 173 (149–189) cm, and a mean (range) weight of 80.1 (54.8–103) kg. Most of the subjects were men (90.6%). No apparent differences were observed in patient characteristics between the two studies.

Pharmacokinetic profiles

A total of 2038 mezigdomide plasma concentrations were available from the two phase I studies and included for modeling. Of these, 22.5% (460/2038) concentrations were below the limit of quantification (BLOQ) and treated as left-censoring data based on the likelihood that BLOQ concentration is less than the LLOQ in the model development.[9] The mean plasma concentrations of mezigdomide were summarized by dose levels and different treatment scenarios (i.e., fed/fasted, and with or without a PPI) at each dose level; the mean concentration-time course plot is shown in Figure 2. Overall, the plasma PK profiles of mezigdomide suggested dose-dependent exposure increases and rapid oral absorption (time to maximum concentration [T_{max}] ranged between 1 and 4 h) over the dose range between 0.4 mg and 3.2 mg, under the fasted condition and in absence of a PPI. Under the fed condition, absorption was delayed with maximum concentration (C_{max}) achieved between 4 and 8 h, whereas the area under the curve (AUC) showed a small increase compared with the fasted condition (Figure 2b). In the subjects co-dosed with mezigdomide and a PPI (i.e., rabeprazole), the PK profile showed substantial apparent decrease in C_{max} and AUC in comparison to that in the subjects dosed with mezigdomide alone (Figure 2c). In addition, the elimination phases of PK profiles appeared to be parallel under all scenarios, suggesting no apparent effect of dose, formulation, food, or a PPI on the elimination rate of mezigdomide in HSs. Additional plots with both concentrations and time on a log scale are included in (Text S2) to better demonstrate PK profiles around T_{max}.

TABLE 1 Summary of demographic characteristics.

	Study I (NCT03803644, *N* = 40)	Study II (NCT04211545, *N* = 24)	Total (*N* = 64)
Age, years, mean [range]	39.8 [18–55]	36.5 [25–53]	38.5 [18–55]
Sex, *n* [%]			
Female	5 [12.5%]	1 [4.2%]	6 [9.4%]
Male	35 [87.5%]	23 [95.8%]	58 [90.6%]
Height, cm, mean [range]	172 [149–187]	175 [160–189]	173 [149–189]
Weight, kg, mean [range]	79.4 [54.8–103]	81.3 [57.4–103]	80.1 [54.8–103]
BMI, kg/m^2, mean [range]	26.8 [20.6–32.6]	26.5 [22.3–32.9]	26.7 [20.6–32.9]
Serum creatinine, μmol/L, mean [range]	85.5 [51.3–110]	86.2 [66.3–112]	85.7 [51.3–112]
Race, *n* [%]			
American Indian or Alaska Native	1 [2.5%]	0 [0%]	1 [1.6%]
Asian	1 [2.5%]	0 [0%]	1 [1.6%]
Black or African American	12 [30%]	14 [58.3%]	26 [40.6%]
White	26 [65%]	10 [41.7%]	36 [56.3%]
Ethnicity, *n* [%]			
Hispanic or Latino	17 [42.5%]	9 [37.5%]	26 [40.6%]
Not Hispanic or Latino	23 [57.5%]	15 [62.5%]	38 [59.4%]

Abbreviation: BMI, body mass index.

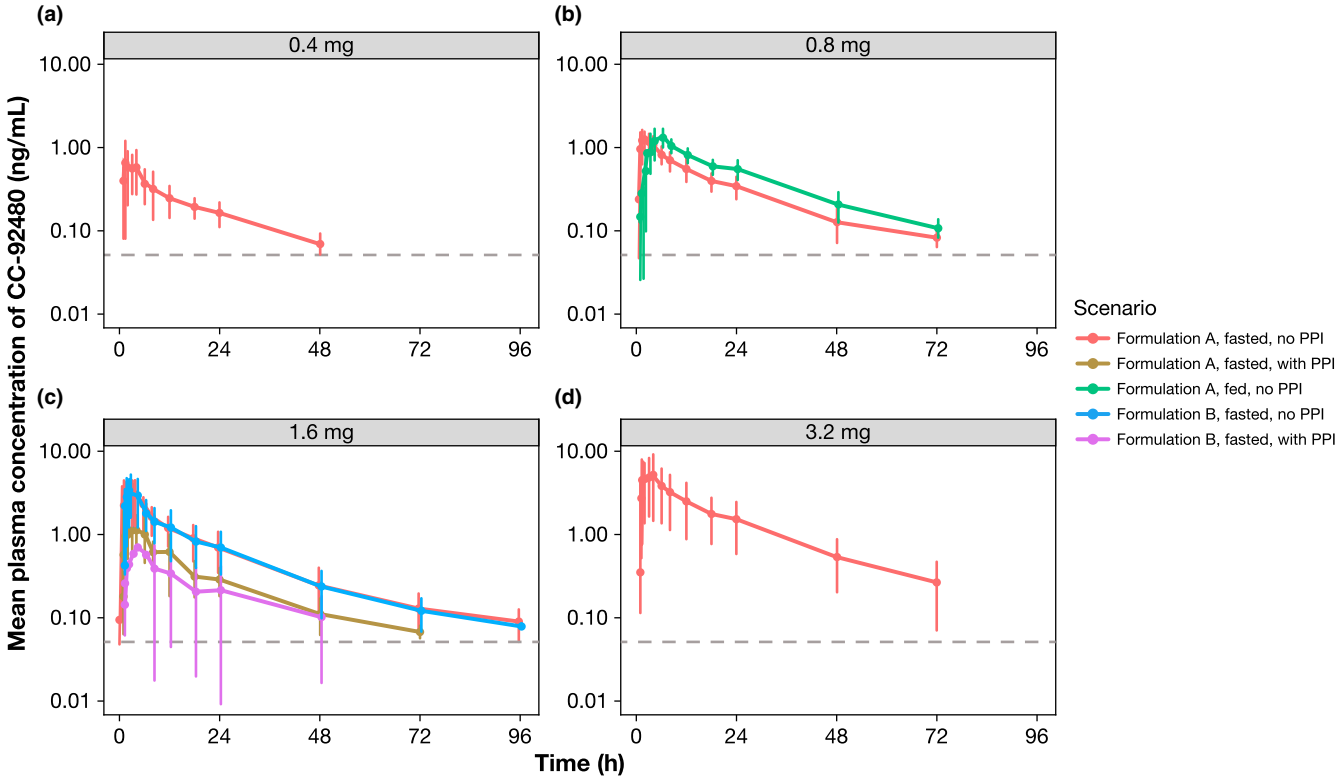

FIGURE 2 Mean plasma concentrations profiles of mezigdomide. Formulation A, test formulation; formulation B, reference formulation; h, hour; PPI, proton pump inhibitor.

Population PK modeling

The structural PK model was selected to be the two-compartment PK model with first-order oral absorption due to its preferrable statistical criteria value (BICc: 3106) in comparison with those of the one-compartment PK model (BICc: 3243) and three-compartment PK model (BICc: 3134). The T_{lag} was incorporated as it significantly improved the model performance (BICc: 2425).

Based on graphical inspection (Figure 2), the food and PPI effects on F and absorption parameters (k_a and T_{lag}) were examined as potential covariates. The PPI effect on k_a was further found to be formulation dependent, whereas inclusion of formulation effects directly on F but not k_a or T_{lag} resulted in improvement of model performance (Table S2).

In addition, covariate effects of sex and baseline body weight on CL were initially incorporated during model building as suggested by Pearson's correlation test and/or analysis of variance (ANOVA) results provided in Monolix. The effect of serum creatinine level (ranging between 51.3 and 112 μmol/L) on CL was also examined to explore potential impacts of renal function on mezigdomide PKs in HSs. The covariate effect evaluation revealed that model performance indicated by BICc was not improved by incorporating the covariate effect of serum creatinine level and sex or body weight on CL, which were thus not included in the final model.

As summarized in Figure 3a, the final population PK parameters were estimated with good precision (i.e., relative standard error ≤ ~30%). The final model suggested moderate to high IIV of CL and V1 (39.9% and 63.4%, respectively), low IOV of T_{lag} (31.0%), and moderate to high IOV in k_a (65.0%). High correlation (0.862) was found between random effects of CL and V1. The good precision in model parameters was confirmed by the bootstrap of resampling results showing relatively narrow 90% confidence intervals from 1000 bootstrap runs (Figure 3a). The convergence assessment indicated that the SAEM algorithm converged to the global maximum of likelihood with the final population PK parameters (Figure S2).

The final population PK model performance was also evaluated using both goodness-of-fit plots and VPC. The goodness-of-fit plots suggest good agreement between observations and model predictions at both the population level (Figure 4a) and the individual level (Figure 4b). The distribution of individual weighted residuals (IWRES) was found to be homogeneously around zero without clear trends between IWRES and time postdose (Figure 4c) or between IWRES and predicted concentrations (Figure 4d). The VPC was conducted with 1000 simulations generated in Monolix and re-plotted in RStudio. The VPC plots reveal that the empirical (i.e., 10th, 50th, and 90th) percentiles of

(a)

Parameter	Value	Stochastic approximation		Bootstrap estimation (90% CI)
		SE	RSE (%)	
Fixed effects				
F_{pop}	1 (fixed)			
CL_{pop} (L/h)	35.10	1.79	5.10	35.7 (33.3 to 38.6)
$V1_{pop}$ (L)	440	37.50	8.52	421 (340 to 481)
Q_{pop} (L/h)	36.80	3.11	8.45	39.7 (31.8 to 68.7)
$V2_{pop}$ (L)	243	15.30	6.28	258 (214 to 360)
ka_{pop} (1/h)	1.18	0.106	8.99	1.04 (0.700 to 1.25)
$Tlag_{pop}$ (h)	0.423	0.014	3.32	0.411 (0.388 to 0.446)
$\beta_{F,FOOD}$	0.234	0.0304	12.9	0.260 (0.196 to 0.322)
$\beta_{F,FORMU}$	−0.236	0.0186	7.88	−0.214 (−0.350 to −0.152)
$\beta_{F,PPI}$	−1.06	0.0232	2.18	−1.09 (−1.22 to −0.899)
$\beta_{Tlag,FOOD}$	1.11	0.0895	8.09	1.12 (0.962 to 1.28)
$\beta_{ka,FOOD}$	−1.15	0.198	17.3	−1.14 (−1.37 to −0.848)
$\beta_{ka,PPIA}$	−0.592	0.191	32.2	−0.544 (−0.751 to −0.374)
$\beta_{ka,PPIB}$	−1.99	0.189	9.48	−1.87 (−2.24 to −1.55)
Standard deviation of the random effects				
ω_{CL}	0.399	0.0325	8.14	0.450 (0.374 to 0.500)
ω_{V1}	0.634	0.0589	9.29	0.656 (0.545 to 0.771)
ω_{Q}	0.262	0.0773	29.5	0.218 (0.158 to 0.395)
ω_{V2}	0.255	0.0434	17.0	0.267 (0.200 to 0.351)
γ_{Tlag}	0.310	0.0258	8.33	0.296 (0.238 to 0.354)
γ_{ka}	0.650	0.0452	6.95	0.568 (0.522 to 0.712)
Correlations				
$corr_{V1,CL}$	0.862	0.0371	4.30	0.894 (0.819 to 0.910)
Error model parameters				
a	0.0257	0.00166	6.46	0.0248 (0.0156 to 0.0293)
b	0.210	0.00450	2.14	0.234 (0.203 to 0.262)

(b)

Extrinsic factor	Model-predicted F ratio of test/reference (90% CI)	Clinically observed AUC_{inf} ratio of test/reference (90% CI)
Fed/fasted	1.30 (1.22 to 1.38)	1.29 (1.19 to 1.38)
PPI/no PPI	0.360 (0.301 to 0.407)	0.398 (0.321 to 0.493) for Formulation A 0.373 (0.288 to 0.484) for Formulation B
Formulation B/ Formulation A	0.798 (0.713 to 0.853)	0.820 (0.700 to 0.960)

FIGURE 3 (a) Population PK parameters. AUC_{inf}, area under the curve from zero to infinity; CI, confidence interval; CL, clearance; *F*, relative bioavailability; k_a, absorption rate constant; PPI, proton pump inhibitor; *Q*, intercompartment clearance; RSE, relative standard error; SE, standard error; T_{lag}, lag time in absorption; *V*1, distribution volume of the central compartment; *V*2, distribution volume of the peripheral compartment; β, covariate effect; γ, inter-occasion variability; ω, inter-individual variability. (b) Summary of model-predicted effects of food, PPI, and formulation on relative bioavailability of mezigdomide in comparison with clinical observed effects in HS. The model-predicted relative bioavailability ratios of test/reference were calculated as $\exp(\beta_{F,FOOD})$, $\exp(\beta_{F,PPI})$, and $\exp(\beta_{F,FORMU})$, for fed/fasted, PPI/no PPI, Formulation B/Formulation A, respectively. AUC, area under the curve; CI, confidence interval; *F*, relative bioavailability; Formulation A, test formulation; Formulation B, reference formulation; PPI, proton pump inhibitor.

observed concentration data at time postdose were well-contained within the 90% prediction intervals of the simulated concentration data (Figure 5), indicating that the final PK model was capable of reproducing both the central tendency and variability in the observed data under different dosing and treatment conditions. Additional

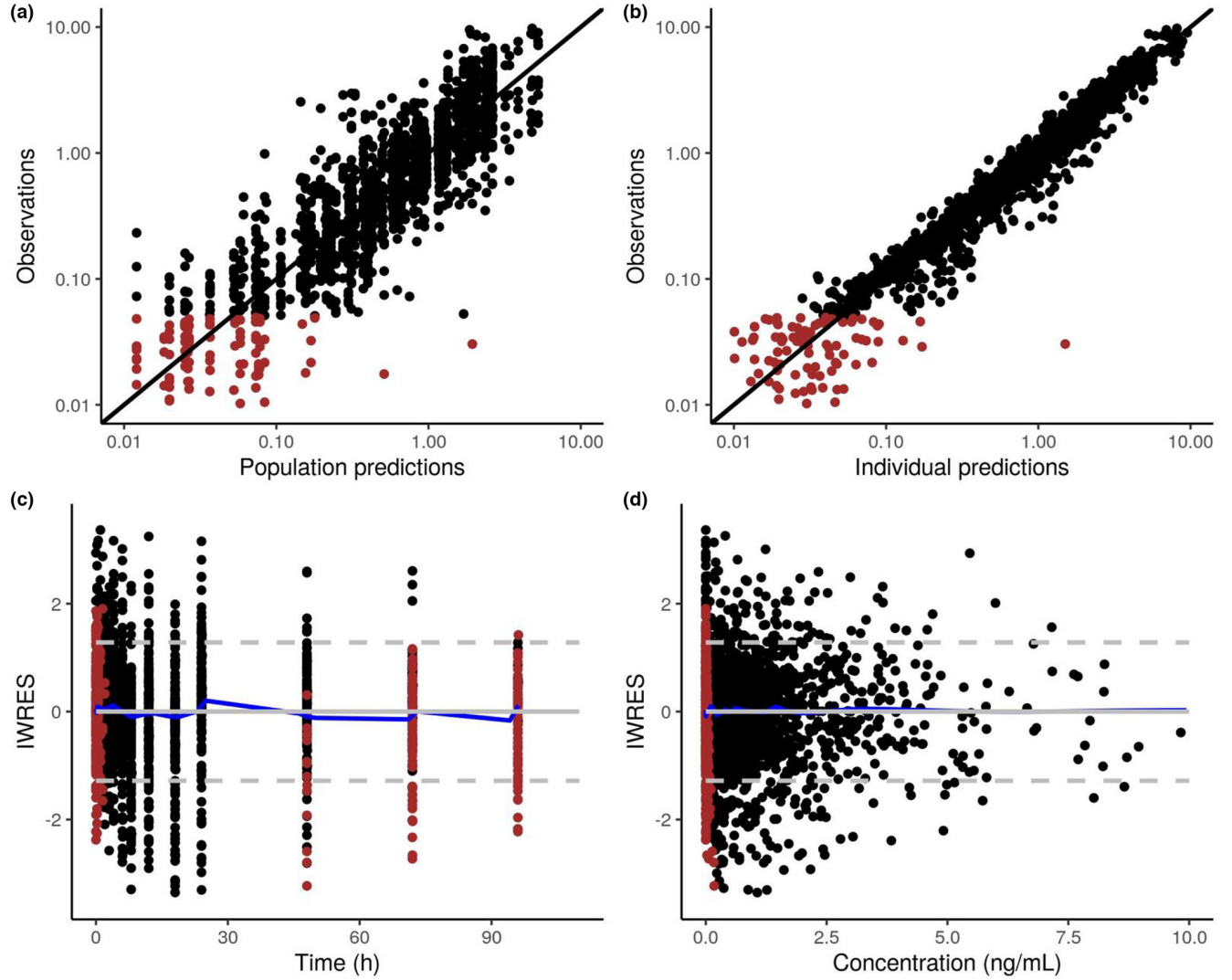

FIGURE 4 Goodness-of-fit plots. Dashed lines represent the 90% predicted percentiles and solid blue splines represent visual cues. Red and black solid dots represent BLOQ and non-BLOQ data, respectively. BLOQ, below the limit of quantification; h, hour; IWRES, individual weighted residuals.

VPC plots with concentrations and time on a log scale are included in (Text S2), suggesting overall adequate modeling fitting around T_{max}.

DISCUSSION

The PKs of mezigdomide in HSs over an eight-fold dose range (0.4–3.2 mg) were sufficiently described by a two-compartment PK model with delayed first-order absorption and first-order elimination, with random effects on CL and V1 at the interindividual level and on F, k_a, and T_{lag} at the interoccasion level. Approximately 20% of the total available plasma concentrations were found to be BLOQ. The BLOQ values were observed at three dose levels including 0.4 mg, 0.8 mg, and 1.6 mg, with the majority (~70%) of BLOQ values observed ≤0.5 h postdose, reflective of the estimated T_{lag} of mezigdomide. A sensitivity analyses suggest that exclusion of BLOQ observations in the model had negligible impact on the model parameter estimation (Table S3).

The model-estimated individual oral clearance of mezigdomide was shown to be dose-independent (Figure 6), suggesting linear dose-exposure proportionality over the 0.4–3.2 mg dose range in HSs.

Using the population PK modeling approach, the potential covariate effects on PK parameters were simultaneously evaluated using the PK data pooled from two separate phase I clinical studies (NCT03803644 and NCT04211545) in HSs. As summarized in Figure 3b, the model-predicted F ratios of fed versus fasted, PPI versus no PPI, and formulation B versus formulation A, recapitulated the clinically observed AUC ratios (data on file).

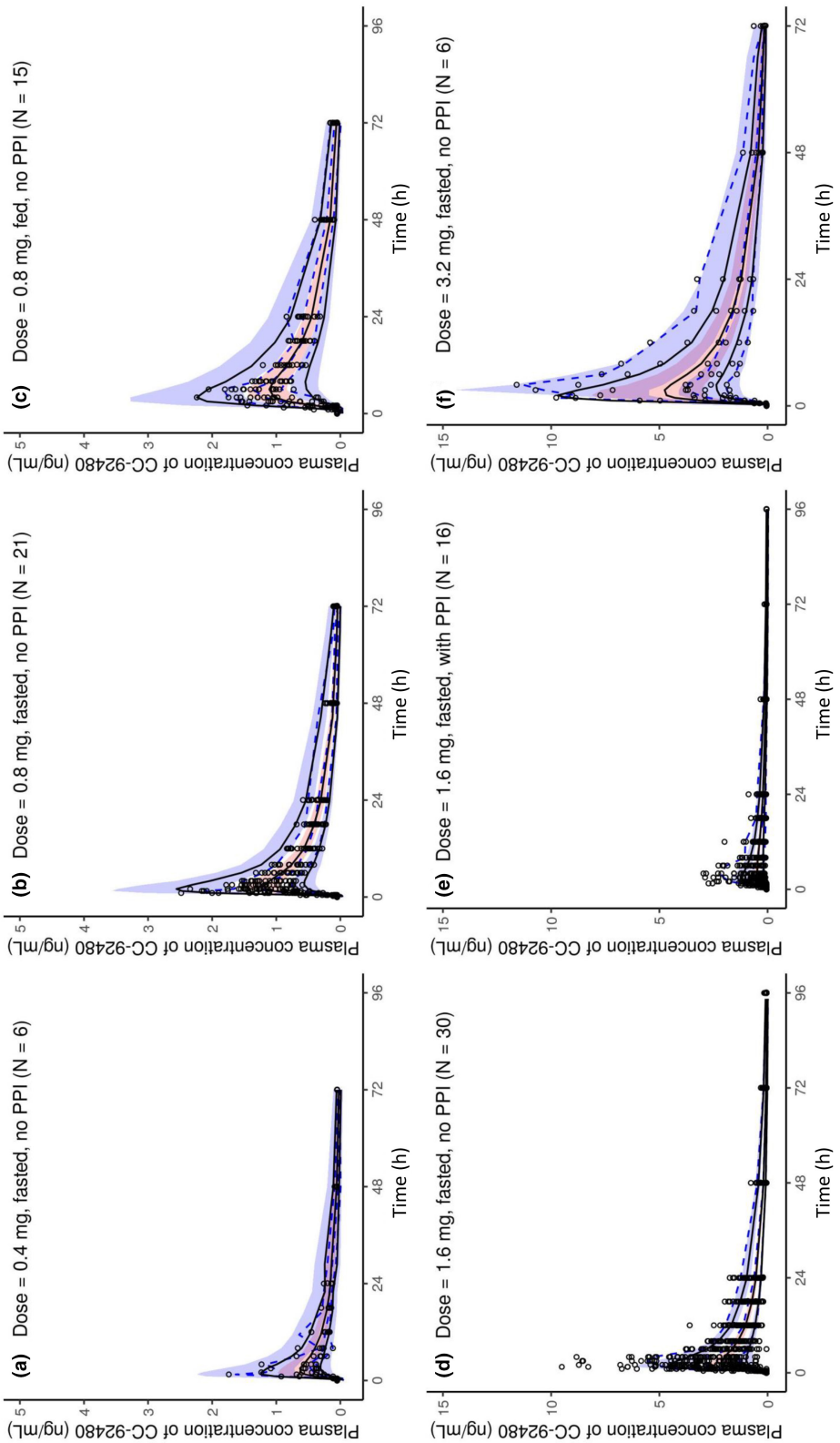

FIGURE 5 Visual predictive check. Data pooled from two studies. Black solid dots represent observed mezigdomide PK data. Blue dashed lines represent median, 10th, 50th, and 90th percentiles of observations. Black solid lines represent 10th, 50th, and 90th percentiles of model-simulated PK profiles. The orange-shaded regions represent the 90% prediction intervals for the 50th percentile of model-simulated PK profiles, whereas the blue-shaded regions represent the 90% prediction intervals for the 10th and 90th percentiles of model-simulated PK profiles. h, hour; PK, pharmacokinetic; PPI, proton pump inhibitor.

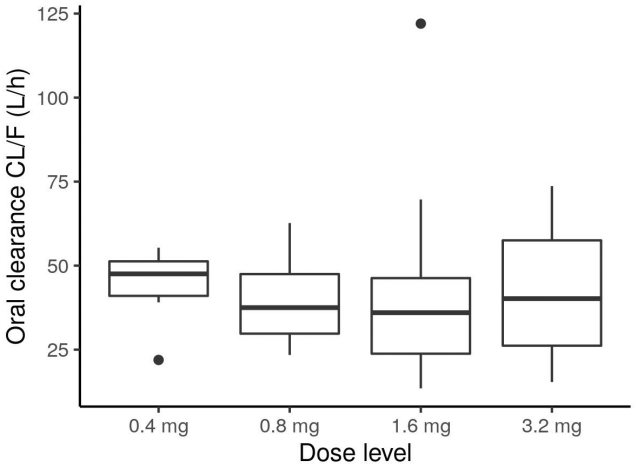

FIGURE 6 Estimated oral clearance across mezigdomide dose levels. CL/*F*, total apparent clearance.

The model-estimated covariate effects suggested that a standard high-fat high-calorie meal[7] resulted in an ~30% increase of the *F*, an increase in T_{lag} by ~0.85 h, and a ~30% decrease in k_a, in comparison with the fasted condition. The model also suggested significant PPI effects on the PK of mezigdomide in HSs co-administered with a PPI (rabeprazole), as reflected by a ~64% decrease in *F* and a ~45% or ~86% decrease in k_a given formulation A or formulation B, respectively. In comparison, the model showed that formulation switching from formulation A (reference formulation) to formulation B (test formulation) resulted in relative minor (~20%) change in *F*. This population PK analysis did not detect potential covariate effects of food or PPI on other drug disposition parameters, including clearance and volumes of distribution, suggesting that food did not impact elimination or distribution of mezigdomide.

It has been widely recognized that interactions between food or PPI and oral drugs may alter systemic exposure due to alterations in gastrointestinal conditions and consequent dissolution and absorption processes of oral drugs.[7,10–12] It is important to adequately estimate effects of these extrinsic factors on absorption parameters because their misspecification may impact estimation of other PK parameters.[13] The impact of food and acid-reducing agents on *F* and PK absorption parameters are of particular relevance to weak-base oral anticancer compounds with pH-limited solubility in vivo. Alterations of gastric pH can lead to substantial changes in their plasma exposure, which can have impact on the anticancer effects.[14,15] The PK-based interactions with food and acid-reducing agents have been reported for other weak-base drugs in the literature.[16–20]

As suggested by this population PK analysis, despite the reduced k_a and prolonged T_{lag}, the relative oral bioavailability with food increased by ~30% in the fed state. The degree of the food effect can be complex and dependent on the physicochemical properties of a drug. In the case of a high-fat meal, although there is a potentially slight pH elevation in the small intestine that might adversely impact absorption of mezigdomide, that effect is likely mitigated due to bile salt-enhanced solubility on mezigdomide and higher gastrointestinal residence time under the fed state.[17,19] The overall impact of a high-fat meal on mezigdomide is considered relatively modest, given the between-subject variability in oral clearance (~40%). In comparison, the substantial effects of a PPI administration on mezigdomide PKs were associated with not only absorption rate but also absorption extent, leading to consequently reduced oral bioavailability and systemic exposures. Thus, the ARAs, which have long-term pharmacodynamic effects (such as long-acting PPIs) when co-dosed with mezigdomide, can lead to substantial exposure decreases and hence co-administration is not recommended. Instead, alternative ARAs such as locally acting antacids taken apart from mezigdomide may be used as appropriate to manage elevated gastric pH in patients.[11]

Covariate effects of intrinsic factors on the other PK parameters including CL and *V*1 were also examined on the basis of Pearson correlation test or ANOVA results in Monolix. The covariate analysis did not identify statistically significant covariate effects of baseline body weight, age, sex, or race on oral clearance or volume of distribution. Additional analysis did not suggest significant effect of renal function, represented by serum creatinine level,[21] on PKs in HSs; however, that estimation may have been limited by a relatively narrow range of serum creatinine values across the HSs enrolled in the trials.

In summary, the plasma PK profiles of mezigdomide of 64 HSs were adequately described by the two-compartment oral PK model with first-order absorption model incorporating a lag time and first-order elimination model. The population PK analysis was used to simultaneously estimate the covariate effects of a high-fat meal and a PPI on PKs, revealing a modest food effect and substantial PPI effect on *F* of mezigdomide. In addition, whereas the food–drug interaction was found to result in delayed absorption characterized by decreased k_a and prolonged T_{lag}, its impact on extent of absorption was found to be modest. Co-administration of a PPI was found to result in decreased k_a and *F*, but no significant changes in T_{lag}. Overall, the population PK model captured the dose-exposure trend, covariate effects of food and a PPI on absorption parameters, and associated variability of the PK parameters. Such a modeling approach provides a systematic framework to integrate data across studies, identify

extrinsic factors including food and PPI covariate effects on PKs, and is being used to guide dose adjustments in clinical studies for mezigdomide.

AUTHOR CONTRIBUTIONS

F.W. and M.L. wrote the manuscript. F.W., L.L., L.C., M.P., and M.L. designed the research. F.W., M.L., L.L., X.W., and L.C. performed the research. F.W., X.W., A.G., and M.L. analyzed the data.

ACKNOWLEDGMENTS

The authors thank Bishoy Hanna for his support in design and implementation of studies NCT03803644 and NCT04211545, and Jessica Katz and Simon Zhou for their review comments during preparation of the manuscript. Editorial assistance was provided by Mauro Locati, PhD, at Excerpta Medica, and was funded by Bristol Myers Squibb.

FUNDING INFORMATION

This study was funded by Bristol Myers Squibb.

CONFLICT OF INTEREST STATEMENT

F.W., L.L., A.G., X.W., L.C., M.P., and M.L. are employees and stockholders of Bristol Myers Squibb.

REFERENCES

1. Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 ligase modulator CC-92480 for the treatment of relapsed and refractory multiple myeloma. *J Med Chem*. 2020;63:6648-6676.
2. Lopez-Girona A, Havens CG, Lu G, et al. CC-92480 is a novel cereblon E3 ligase modulator with enhanced tumoricidal and immunomodulatory activity against sensitive and resistant multiple myeloma cells. *Blood*. 2019;134(suppl 1):1812.
3. Richardson PG, Ocio E, Raje NS, et al. CC-92480, a potent, novel cereblon E3 ligase modulator (CELMoD) agent, in combination with dexamethasone (DEX) and bortezomib (BORT) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): preliminary results from the phase 1/2 study CC-92480-MM-002. *Blood*. 2021;138(suppl 1):2731.
4. Richardson PG, Trudel S, Quach H, et al. Mezigdomide (CC-92480), a potent, novel cereblon E3 ligase modulator (CELMoD), combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): preliminary results from the dose-expansion phase of the CC-92480-MM-001 trial. *Blood*. 2022;140(suppl 1):1366-1368.
5. ClinicalTrials.gov identifier: NCT05519085. A study to evaluate CC-92480, bortezomib and dexamethasone (480Vd) versus pomalidomide, bortezomib and dexamethasone (PVd) in participants with relapsed or refractory multiple myeloma (RRMM) (Successor-1). Updated December 9, 2022. https://clinicaltrials.gov/ct2/show/NCT05519085. Accessed December 11, 2022
6. ClinicalTrials.gov Identifier: NCT05552976. A study to evaluate CC-92480 in combination with carfilzomib and dexamethasone (480 Kd) versus carfilzomib and dexamethasone (Kd) in participants with relapsed or refractory multiple myeloma (SUCCESSOR-2) (SUCCESSOR-2). Updated December 9, 2022. https://clinicaltrials.gov/ct2/show/NCT05552976. Accessed December 11, 2022
7. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Guidance for industry. Assessing the effects of food on drugs in INDs and NDAs — clinical pharmacology considerations. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations. Draft published February 2019. Accessed December 11, 2022
8. Traynard P, Ayral G, Twarogowska M, Chauvin J. Efficient pharmacokinetic modeling workflow with the MonolixSuite: a case study of remifentanil. *CPT Pharmacometrics Syst Pharmacol*. 2020;9:198-210.
9. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. *AAPS J*. 2009;11:371-380.
10. Singh BN. Effects of food on clinical pharmacokinetics. *Clin Pharmacokinet*. 1999;37:213-255.
11. Patel D, Bertz R, Ren S, Boulton DW, Någård M. A systematic review of gastric acid-reducing agent-mediated drug–drug interactions with orally administered medications. *Clin Pharmacokinet*. 2020;59:447-462.
12. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. Evaluation of gastric pH-dependent drug interactions with acid-reducing agents: study design, data analysis, and clinical implications. https://www.fda.gov/media/144026/download. Draft published November 2020. Accessed December 11, 2022
13. Jaber MM, Al-Kofahi M, Sarafoglou K, Brundage RC. Individualized absorption models in population pharmacokinetic analyses. *CPT Pharmacometrics Syst Pharmacol*. 2020;9:307-309.
14. U.S. Food and Drug Administration. *XELODA® (capecitabine) [package insert]*. Roche Laboratories Inc; 2001. https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/20896S1011lbl.pdf. Revised September 7, 2001. Accessed December 11, 2022
15. Lu T, Fraczkiewicz G, Salphati L, et al. Combining "bottom-up" and "top-down" approaches to assess the impact of food and gastric pH on pictilisib (GDC-0941) pharmacokinetics. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:747-755.
16. Willemsen AE, Lubberman FJ, Tol J, et al. Effect of food and acid-reducing agents on the absorption of oral targeted therapies in solid tumors. *Drug Discov Today*. 2016;21:962-976.
17. Koziolek M, Alcarob S, Augustijns P, et al. The mechanisms of pharmacokinetic food-drug interactions – a perspective from the UNGAP group. *Eur J Pharm Sci*. 2019;134:31-59.
18. Del Re M, Omarini C, Diodati L, et al. Drug-drug interactions between palbociclib and proton pump inhibitors may significantly affect clinical outcome of metastatic breast cancer patients. *ESMO Open*. 2021;6:100231.
19. Sun W, Klamerus KJ, Yuhas LM, et al. Impact of acid-reducing agents on the pharmacokinetics of palbociclib, a weak base with pH-dependent solubility, with different food intake conditions. *Clin Pharmacol Drug Dev*. 2017;6:614-626.
20. Zhang L, Wu F, Lee SC, Zhao H, Zhang L. pH-dependent drug–drug interactions for weak base drugs: potential implications for new drug development. *Clin Pharmacol Ther*. 2014;96:266-277.

21. Ahmed MA, Kalaria SN, Younis IR. Concordance of exposure changes because of renal impairment between results of dedicated renal impairment studies and population pharmacokinetic predictions. *J Clin Pharmacol*. 2021;61:1324-1333.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wu F, Liu L, Gaudy A, et al. Model based assessment of food and acid reducing agent effects on oral absorption of mezigdomide (CC-92480), a novel cereblon E3 ligase modulator. *CPT Pharmacometrics Syst Pharmacol*. 2023;12:1473-1484. doi:10.1002/psp4.13024